

Clinicopathological Features of Primary Gastric Lymphoma

JYRKI MÄKELÄ, MD,^{1*} TUOMO KARTTUNEN, MD,² HEIKKI KIVINIEMI, MD,¹ AND SEPPÖ LAITINEN, MD¹

¹Department of Surgery, University of Oulu, Oulu, Finland

²Department of Pathology, University of Oulu, Oulu, Finland

Background and Objectives: Surgery has been the mainstay of the treatment of primary gastric lymphoma, but the value of surgical treatment needs reevaluation.

Methods: Thirty-two patients with primary non-Hodgkin B-cell lymphoma of the stomach were examined retrospectively to evaluate prognostic factors and their impact on survival. All patients had undergone abdominal exploration for radical surgery between 1979 and 1992. The prognostic factors in view of survival after treatment were determined with both univariate and multivariate analyses.

Results: The resectability rate was 66% (21/32) and radical resections had been performed on 53% (17/32). The overall median survival was 65 months and the overall 5-year survival was 56%. The 5-year survival rates related to a modified Ann Arbor classification as follows: I 1E, 86%; I 2E, 100%; II 1E, 44%; II 2E, 37%; IIIE, 20%; and IVE, 0%. Univariate analysis using Kaplan-Meier estimates showed that radical surgery, Ann Arbor stage, patient's age, and lymph node involvement were significant prognostic factors. According to Cox proportional regression analysis, only Ann Arbor stage, radical surgery, and age were significant independent variables.

Conclusions: According to our experience, surgery is still needed for the treatment of primary gastric lymphomas, but the benefits of primary chemotherapy or adjuvant chemotherapy using cytotoxic drugs must be determined in large prospective controlled trials.

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KEY WORDS: primary gastric lymphoma; therapy; staging; prognosis

INTRODUCTION

Enthusiasm for primary chemotherapy and multimodality therapies for primary gastric lymphoma has led to the avoidance of gastric resection and placed it in a role of salvage therapy for life-threatening complications or for treatment of other therapy resistant disease. Recently, Koch et al. [1] suggested that the value of surgery in treatment of primary gastric lymphoma should be reexamined, because they did not find any difference in therapeutic outcome between surgically or conservatively treated patients in a prospective study of primary gastrointestinal lymphoma. On the other hand, the results of long-term follow-up after curative surgery for early gastric lymphoma favorably compare to those reported with

the use of primary chemotherapy and radiotherapy and suggest that surgery remains the best frontline therapy for early gastric lymphoma [2].

Primary lymphoma of the gastric mucosa has long accounted for only 1–7% of all gastric malignancies [3,4] but its incidence is increasing in Western countries. The report from the Surveillance Epidemiology and End Results Committee found a 2-fold increase in the age-adjusted incidence limited to people over 60 years of age

*Correspondence to: Jyrki Mäkelä, MD, Department of Surgery, University of Oulu, Kajaanintie 52A, FIN-90220 Oulu, Finland. Fax No.: (358) 8-315-5318.

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in the United States [5]. This makes the treatment problem of this rare disease more important.

Gastric lymphoma has long been one of the main interests of the Department of Pathology of Oulu University Hospital, and all our gastric lymphomas have been retyped according to the classification of Isaacson and restaged using a modification of the Ann Arbor classification for practical reasons in 1995 [6]. We also found it necessary to review our experience on clinical presentation, staging, management, and results of long-term follow-up.

MATERIALS AND METHODS

The data represent a retrospective review of all patients diagnosed and treated for primary gastric lymphoma during the years 1979–1992 at Oulu University Hospital. All patients were evaluated for surgery in the Department of Surgery and the histological examinations were performed in the Department of Pathology. Of the 32 patients, 18 were men and 14 were women. The mean age of the study group was 62 ± 16 years (range: 27–85) and that of men 59 ± 17 years (range: 27–85) and of women 67 ± 14 years (range: 29–81).

Primary gastric lymphomas were included in the study according to the following criteria: (1) the lymphoma was definitive on histological diagnosis and all those diagnosed were reviewed; (2) the tumor mainly affected the stomach with or without involvement of regional lymph nodes or adjacent organs; (3) no peripheral or mediastinal lymphadenopathy was present at the early stage of the disease; (4) the white blood cell count was within normal range.

The histological diagnosis was based on 4 μ m sections made from original formalin-fixed, paraffin-embedded specimens stained with hematoxylin-eosin (H&E). Additional sections were stained with L26 antibody (CD20; Dako, Copenhagen, Denmark) and UCHL1 (CD45RO; Dako) to verify the cell lineage of tumor and intraepithelial lymphocytes. Gastric lymphomas were staged by the Ann Arbor classification with the modification proposed by Musshoff [7] for non-Hodgkin lymphoma as follows: (1) I 1E, tumor confined to mucosa or submucosa; (2) I 2E, tumor extending beyond submucosa; (3) II 1E, tumor with spread to regional lymph nodes; (4) II 2E, tumor with nodal involvement beyond regional lymph nodes; (5) III E, tumor with spread to both sides of diaphragm; (6) IV E, tumor with spread to other intra-abdominal organs. Tumors were typed according to the classification of Isaacson [8] and the depth of invasion into the gastric wall was reevaluated also.

According to the classification of Isaacson, 6 patients presented with low-grade and 3 patients with high-grade B-cell gastric lymphomas of mucosa-associated lymphoid tissue (MALT), 10 patients with other types of low-grade, and 13 patients with other types of high-grade

B-cell gastric lymphomas. Using the Ann Arbor gastric lymphoma staging 6 tumors (19%) were I 1E, 8 (25%) I 2E, 5 (16%) II 1E, 2 (6%) II 2E, 8 (25%) III E, and 3 (9%) IV E.

The clinical findings regarding preoperative symptoms, loss of weight, diagnostic delay, localization of the disease, size and macroscopic appearance of the tumor, resectability, operations performed, radiotherapy, chemotherapy, recurrence of the disease, and survival were reviewed from patient records. Radical resection here denotes removal of all macroscopic tumor.

All patients underwent laparotomy for evaluation of possible removal of the tumor and exploration for the extension of the disease. Twelve patients underwent radical and 1 palliative total gastrectomy, 4 radical and 3 palliative gastric resection, 1 had a palliative gastric bypass procedure, and 11 had laparotomy and biopsy. In all 20 resected cases N1 lymphadenectomy was performed and in 13 cases splenectomy was performed. Of the 11 patients who had laparotomy only, 4 patients had both chemotherapeutic multidrug therapy and radiotherapy of 40 Gy, 4 had radiotherapy of 40 Gy, 2 had multidrug chemotherapy, and 1 was treated conservatively. In addition, 4 patients received adjuvant radiotherapy of 40 Gy and 2 patients chemotherapeutic multidrug therapy after total gastrectomy, 2 patients postoperative chemotherapy after gastric resection, and 1 after gastric bypass procedure.

The follow-up time ranged from 3 months to 21 years (median: 7 years) and all patients were followed up continuously until December 1997 or until death, in the outpatient clinic of the oncologic clinic of our hospital. Survival rates were analyzed using Kaplan-Meier survival estimates and survivals were compared using one-sided log-rank tests. A multivariate analysis of factors influencing survival was determined by the Cox regression analysis. All tests were performed using the SPSS for Windows 95 statistical package.

RESULTS

The most common clinical symptom at presentation was epigastric pain (24, 75%), followed by a weight loss of more than 5 kg (17, 53%) and upper gastrointestinal bleeding (4, 13%).

The mean diagnostic delay was 7 months (range: 1–24 months) and the diagnosis was confirmed by preoperative biopsy in 30 cases (94%) and by perioperative biopsy in 2 cases (6%).

The location of lymphoma was as follows: antrum, 9 (28%); antrum and corpus, 11 (34%); corpus, 6 (19%); corpus and cardia, 4 (13%); cardia, 1 (3%); and fundus, 1 (3%). In 8 cases, the diameter of the tumor was <5 cm; in 10 cases, 5–10 cm; and in 14 cases >10 cm.

The macroscopic appearance of the lesion was infiltrating in 15 cases (47%), ulcerating in 9 (28%), polypoid

TABLE I. Characteristics of Patients Permanently Cured of Gastric Lymphoma

No.	Age (years)	Ann Arbor classification	Isaacson classification	Depth of invasion	Lymph node involvement	Surgery	Radiotherapy	Chemotherapy
1	71	IE 2	High	Musculature	–	Gastrectomy	–	–
2	56	IE 2	High	Serosa	–	Resection	–	–
3	54	IE 1	Low	Submucosa	–	Gastrectomy	–	–
4	27	IE 1	Low	Submucosa	–	Gastrectomy	–	–
5	65	IE 1	High	Submucosa	–	Gastrectomy	–	–
6	29	IE 1	Low	Mucosa	–	Gastrectomy	–	–
7	59	IE 1	High	Mucosa	–	Gastrectomy	–	–
8	55	IE 2	Low	Serosa	–	Resection	–	–
9	64	IE 2	Low	Serosa	–	Gastrectomy	+	–
10	64	IIIE	High	Serosa ^a	+	Laparotomy	+	+
11	63	IIIE 1	High	Serosa	–	Gastrectomy	–	+
12	26	IIIE 2	Low	Serosa ^a	+	Laparotomy	+	–
13	72	IIIE 1	High	Serosa	+	Gastrectomy	–	–
14	41	IE 2	Low	Serosa	+	Gastrectomy	–	–
15	30	IIIE 2	High	Serosa	–	Gastrectomy	–	–
16	31	IE 2	Low	Musculature	–	Resection	–	–

^aThe growth extends beyond the serosa into the pancreas.

in 4 (13%), and polypoid and ulcerating in 4 (13%), respectively.

The resectability rate was 21/32 (66%) and radical resections were performed in 17 cases (53%). Postoperative complications developed in 9% (3/32) of the patients and they consisted of 2 intra-abdominal abscesses and 1 wound rupture. Thirty-day mortality was 0%, but 3 patients died within 5 months after the diagnosis of causes unrelated to surgery. Two of them died without any complications from far-advanced disease, but one high-risk patient developed gastric bleeding from the tumor bed 2 months after palliative CHOP chemotherapy and all conservative treatment efforts were ineffective.

Two patients developed recurrence after radical resection and 4 after palliative resection. Of the 2 patients who had radical resection, the first presented with II 1E tumor and received radiotherapy of 40 Gy for recurrence; the other presented with I 2E tumor and underwent total gastrectomy for local recurrence 18 months after primary gastric resection. The first patient died 5 years after primary surgery and the other has survived 9 years disease free following reresection. Of the 4 patients who underwent palliative surgery, 3 received radiotherapy of 40 Gy and 1 underwent palliative intestinal resection. The patient with II 1E tumor who underwent primary total gastrectomy received radiotherapy of 40 Gy for histologically proven recurrence and is alive 8 years after surgery. All other patients in this group have died within 3 years.

The overall actuarial survival was 81% at 1 year, 62% at 3 years, and 56% at 5 years, and the median survival was 65 months. Fourteen permanently cured patients had undergone radical surgery. One patient has experienced 8 years of disease-free survival after radical radiotherapy of 40 Gy and the other 13 years of disease-free survival

after radical radiotherapy of 40 Gy and CHOP chemotherapy (Table I).

The 5-year survival rates according to the Ann Arbor classification were: I 1E, 86%; I 2E, 100%; II 1E, 44%; II 2E, 37%; IIIIE, 20%; and IVE, 0%. When I 1E and I 2E groups were combined, the 5-year survival rate was 93%, and when II 1E and II 2E groups were combined it was 40%. The 5-year survivals were 62% for low-grade malignancy and 50% for high-grade malignancy. According to the depth of the invasion into the gastric wall, cumulative 5-year survivals were as follows: tumors with involvement of mucosa, 80%; submucosa, 75%; musculature, 75%; serosa, 76%; and beyond the serosa, 18%. After radical surgery the 5-year survival was 88% and after palliative surgery was 50%.

Univariate analysis using Kaplan-Meier estimates indicated that sex, diagnostic delay, loss of weight, location of primary tumor, size of tumor, Isaacson classification, serosal involvement, radiotherapy, and chemotherapy were insignificant variables, whereas radical surgery ($P = 0.019$), Ann Arbor classification ($P = 0.025$), and age under 50 years ($P = 0.049$) were good prognostic factors and age over 70 years ($P = 0.014$) and lymph node involvement ($P = 0.036$) were bad prognostic factors.

Cox proportional regression analysis of all the above-mentioned variables showed that only Ann Arbor classification ($P = 0.0020$; Fig. 1), radical surgery ($P = 0.0041$; Fig. 2), and old age ($P = 0.0186$; Fig. 3) were significant independent variables.

DISCUSSION

The rarity of gastric lymphoma leads to controversy regarding the best form of therapy and decision of the

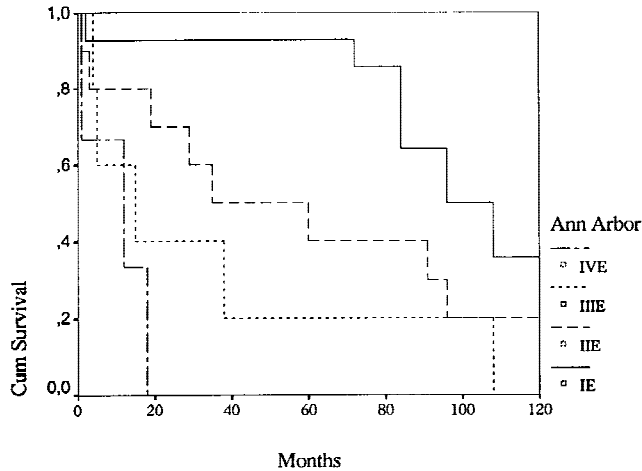


Fig. 1. Kaplan-Meier survival curves related to Ann Arbor classification ($P < 0.025$, log-rank test).

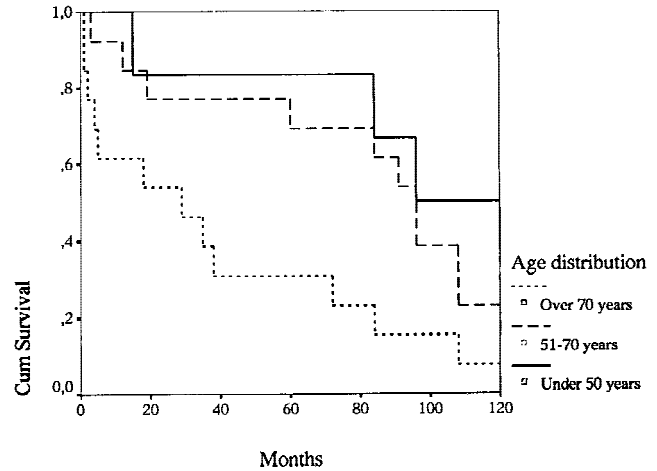


Fig. 3. Kaplan-Meier survival curves related to age ($P < 0.018$, log-rank test).

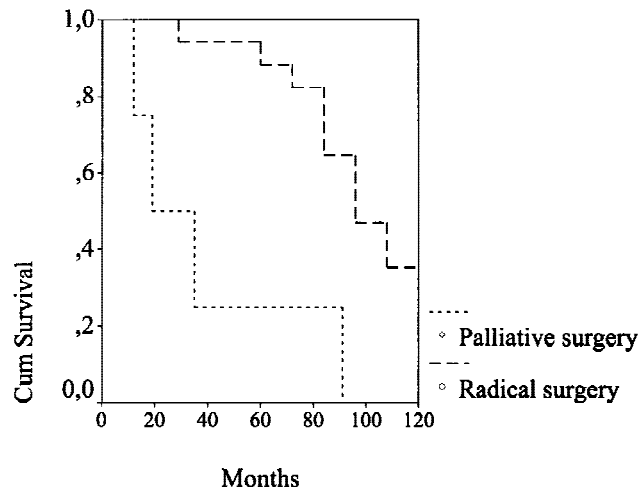


Fig. 2. Kaplan-Meier survival curves related to surgical treatment ($P < 0.019$, log-rank test).

optimal therapeutic approach must be made in prospective multicenter trials.

Adequate staging of the disease is of the utmost importance, if only nonsurgical treatment modalities are chosen. When patients with proven gastric lymphoma are subjected to an extensive diagnostic assessment that includes computed tomography of the chest and abdomen, bone marrow aspirate and biopsy, laryngoscopy, and possibly endoscopic ultrasonography, it is unlikely that surgical exploration of the abdominal cavity would lead to a significant change in the staging of the disease [9]. If surgery is no longer regarded mandatory for staging, conservative treatment can be a good option in stages IE and IIE [1,10,11].

The results of our retrospective series favor radical surgery, but resections could be performed in only 66% of the cases, when the resectability rate usually ranges from 66 to 88% [9]. Usually the cause of nonresectability

was far-advanced disease where limited local resection of tumor bulk in the stomach seemed unadvisable. None of our patients died postoperatively, but one patient succumbed to gastrointestinal bleeding after CHOP chemotherapy. This patient also developed thrombocytopenia and this made the hemorrhage more difficult to manage. The chemotherapy protocols are associated with 1–10% treatment-related mortality [9], depending on the aggressiveness of the protocol, and this can add considerably to treatment-related mortality.

We have had the intention of removal of all tumor tissue with regional lymph nodes but we have not performed formal N2 dissection in all cases. Surgical treatment with a wide resection of the stomach and extensive lymph node dissection is recommended by Kitamura et al. [12], but others regard adjuvant chemotherapy necessary, both for local and systemic control of the disease, either in selected cases [13] or in all cases [14]. Tondini et al. [15] even regard chemotherapy as a safe and effective treatment for primary gastric large-cell lymphoma in which most patients can probably be spared surgical gastrectomy. This means that extensive abdominal dissection of lymph nodes is not needed in primary gastric lymphoma if effective additional treatment alternatives are offered.

Our overall 5-year survival was 56% and this correlates well with the 57% of meta-analysis of 178 articles listed on Medline between January 1974 and April 1995 [16], although even better results (83.5% overall 5-year survival rate) have been presented [17]. The 5-year survival rates by Ann Arbor stage in the meta-analysis of Brands et al. [16] were 77% for stage IE, 70% for stage II 1E, 37% for stage II 2E, 31% for stage IIIE, and 27% for stage IVE. Our 44% 5-year survival for stage II 1E and 0% for stage IVE are not in line with that. The principal reason for this is a low radical resection rate: 20% in stage II 1E and 0% in stage IVE, and of course

the fact that no formal adjuvant therapy regimen has been used in these patients. This figure necessitates more intense attention in the future and surgical management must be followed by a planned adjuvant therapy that may produce complete remission and long-term disease-free survival in patients with stage II disease [18] or even in patients with relapse [19].

The survival probability for low-grade B-cell gastric lymphomas is better than for tumors with secondary high-grade transformation or for primary high-grade lymphomas, whereas the two high-grade groups are not different [20]. Histological classification into low-grade and high-grade separates two distinctive groups of gastric MALT lymphoma which show striking clinical and prognostic differences [21], although the clear difference in this study did not reach statistical significance.

In the U.S. study of Rackner et al. [22], multivariate analysis showed that lower stage of the disease, surgical resectability of lymphoma, and patient age were significant prognostic factors and the same variables proved to be significant here. Major prognosticators for survival in the European study of Radaszkiewicz et al. [23] were low-grade histology, low depth of infiltration, low stage of the disease, and radical resectability. The clinical stage is the sole prognostic factor with proven impact on survival in some studies [24,25], and it can be regarded as the most important prognostic factor.

In conclusion, stage of the disease, radical surgery, and age of the patient are significant variables affecting long-term survival of patients presenting with primary B-cell malignant lymphoma of the stomach, but the mode of adjuvant therapy urgently needs exact information from prospective randomized trials.

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